

The Treatment of Hypertension with Hexamethonium

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Hexamethonium by subcutaneous injection in doses of 10 to 75 mg. of the ion every 8 or 12 hours produced significant reductions of arterial pressure and symptomatic improvement in a high percentage of patients with benign or malignant hypertension. Methods for preventing tolerance and undesirable side effects are presented, and the advantages as well as the limitations of hexamethonium therapy are discussed.

IN 1948 Paton and Zaimis¹ introduced a series of polymethylene bistrimethylammonium compounds of which the decamethonium (C10) member exhibited curariform properties while the penta- and hexamethonium (C5 and C6) compounds produced a blockade of all autonomic ganglions.

Arnold, Goetz and Rosenheim² and Burt and Graham³ demonstrated the marked vasodilator and hypotensive properties of penta-methonium in man. Kay and Smith⁴ noted a marked reduction of gastric acidity after hexamethonium in patients with peptic ulcer, this effect apparently being due to inhibition of the parasympathetic nervous system. Favorable reports⁵⁻⁸ have appeared concerning the use of C5 and/or C6 in the treatment of essential hypertension.

Previous studies in this laboratory indicated that hexamethonium, C6, produced greater vasodilatation in the toes than either tetraethylammonium or Priscoline.⁹ Quantitative measurements of the increase in foot blood flow

after 50 to 100 mg. of C6 ion in normal subjects suggested that this compound produced nearly complete blockade of the sympathetic outflow to the foot¹⁰ and was, therefore, considerably more potent than previously known vasodilator agents.¹¹ The present communication outlines our experience to date with C6 in the treatment of hypertension. The dosages of hexamethonium given in this paper refer to the amount of C6 ion rather than of the salt hexamethonium dibromide.

TIME-DOSE RELATIONSHIPS

Following the intravenous administration of 5 to 50 mg. of C6 ion (9.6 to 96 mg. of hexamethonium dibromide) the cardiovascular effects of the drug appeared within two to three minutes and quickly reached a maximum within 10 minutes or less. These effects consisted of a reduction of blood pressure and increase of heart rate, both of variable degree, as well as a consistent marked postural hypotension. Following the larger doses there also was a marked increase of foot blood flow and digital skin temperature. The peak of these effects usually lasted 15 minutes after which there was a gradual waning over a period of 5 to 10 hours. The heart rate usually increased only slightly and at times actually decreased.

By the intramuscular and subcutaneous routes responses occurred at 15 to 30 minutes following injection and persisted for a period similar to that observed after intravenous administration.

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EFFECT OF ORAL ADMINISTRATION OF HEXAMETHONIUM

A previously untreated 49 year old man with essential hypertension was given 25 mg. of C6 intravenously with a reduction of blood pressure from 220/120 to 160/95 and a further fall to 110/70 on sitting up in bed. The next day he was given 0.5 Gm. of C6 ion orally in the form of the dibromide salt. One hour later the blood pressure had fallen from 225/125 to 190/115 with a further reduction to 150/110 on standing upright. Two hours later the blood pressure rose to the control values and the postural hypotension had disappeared.

The next morning the patient was given 0.8 Gm. of C6 ion after breakfast. There was no significant reduction of arterial pressure until three hours after the dose had been taken when the blood pressure was unchanged with the patient in the supine position but in the erect position it fell from 210/130 to 160/115. At five hours the patient complained of feeling cold (a reaction we have noted when the increase in peripheral blood flow is intense). The blood pressure was 170/115 supine and 120/90 erect. At eight hours he felt weak and listless and was unable to stand without faintness. The blood pressure was 160/110 supine and 110/80 on sitting up in bed. At 10 hours the blood pressure supine was 130/80 and the patient developed nausea and vomiting. Following this the blood pressure rose gradually and at 24 hours it was 180/100 with no postural hypotension. Thus, a dose of 0.5 Gm. had produced only a transient and minimal response whereas the next day a dose of 0.8 Gm. had resulted in a delayed and profound degree of autonomic blockade. Similar unpredictable responses were seen in two other cases who were given single daily doses of C6 orally.

Three hospitalized patients who had exhibited satisfactory hypotensive responses to parenteral C6 in doses varying from 10 to 25 mg. twice daily were given the drug orally in amounts varying from 0.25 to 1.0 Gm. of C6 ion every 12 hours for periods ranging from five days to two weeks. In all of these patients the hypotensive response usually was considerably less marked and more fleeting than after

parenteral dosages. It was apparent that these large oral doses were insufficient, suggesting that almost the entire amount had been destroyed in the gastrointestinal tract. However, on occasion marked reductions of blood pressure occurred accompanied by severe postural hypotension suggesting that the rate of destruction and absorption was sporadic and, hence, unpredictable.

TOXIC REACTIONS

The "toxic reactions" to the drug appeared to be due entirely to the blockade of autonomic ganglions. In hypertensive, elderly and debilitated patients sudden and profound reductions of blood pressure to collapse levels have occurred even when the patients were in the supine position. Parenteral doses as small as 10 mg. may precipitate these marked hypotensive reactions. Almost always they occurred after the initial injection and, when dosages were repeated several times per day, the blood pressure reduction was more moderate. However, if the drug was discontinued for four or five days or longer an injection of C6 might be followed again by a marked fall of arterial pressure. In general, the greater the interval between injections of C6 the more marked and long lasting the reduction of blood pressure following each injection.

All patients exhibited marked postural hypotension which persisted for four to six hours or even longer but was severe only during the first three hours after the drug. During continued administration of C6, particularly if the drug was given at frequent intervals (four to six hours apart) the postural effect diminished in intensity. With less frequent administration (8 to 12 hour intervals) considerable but not disabling postural hypotension was retained for as long as our observations have been carried out (five months).

Approximately two-thirds of the hypertensive patients complained of constipation. In addition, in four cases a condition resembling paralytic ileus occurred during the first week of treatment which was manifested by distention, obstipation, absence of peristaltic sounds on auscultation of the abdomen and nausea. In

one instance fluid levels were seen in the small bowel by roentgenography.

The constipation and ileus apparently were due to the marked inhibition of gastrointestinal tract motility produced by the blockade of the autonomic nervous system, particularly the parasympathetic system.¹² For this reason we have used more recently, to restore bowel motility, parasympathomimetic agents, the most satisfactory of which has been the urethane of β -methylcholine (Urecholine) in doses of 5 to 20 mg. (average dose 10 mg.) under the tongue two to three times per day. If constipation continued despite tolerated doses of this drug, laxatives such as mineral oil and magnesium hydroxide were used in addition. However, since Urecholine has been used no further cases of ileus have been encountered. The drug also prevented the dryness of the mouth complained of in a few patients.

Four hypertensive patients complained of urinary retention. This difficulty also occurred early in treatment and disappeared following temporary reduction of dosage. It probably also is due to parasympathetic blockade and has not been observed since the introduction of parasympathomimetic agents into the treatment regimen.

DOSAGE ADJUSTMENT

In all cases over the age of 40 and in all debilitated or hypertensive patients the initial dosage level was determined as follows: while the blood pressure was being recorded once per minute in the opposite arm, the patient being propped up slightly in bed, C6 was injected at a rate of 1 mg. of the ion per minute until a total of 10 mg. had been administered. If there was no significant fall of blood pressure the rate of administration was increased to 2 mg. per minute until an additional 10 mg. had been given and then at a rate of 5 mg. per minute to a total of 50 mg. As soon as a slight reduction of blood pressure occurred the injection was temporarily halted for two to three minutes in order to determine whether a further fall of pressure would occur.

If, at any time during this trial period, there was a profound fall of blood pressure, the pillow was removed from beneath the patient's head

and he was placed in a head-down position by tilting the foot of the bed on shock blocks. The lower extremities were elevated and passively exercised. If this failed to restore the blood pressure the intravenous administration of 2 to 5 mg. of phenylephrine hydrochloride (Neosynephrine) intravenously quickly elevated the blood pressure to normal levels. These severe hypotensive reactions occurred prior to the institution of the method for determining the initial dosage outlined above. They were sufficiently frequent to make it obligatory that a physician administer the first dose of the drug and that an assistant follow the blood pressure response in order to arrive at a dose level that was safe for the particular case. When these precautions were taken severe collapse reactions have been avoided.

After the effective dose had been determined, this amount was administered every 8 to 12 hours by subcutaneous injection since shorter intervals between doses seemed impractical for chronic therapy of hypertension. The initial dosage level seldom was effective beyond several days so that it was necessary to increase each dose by an amount of 5 to 15 mg. and further increases were made as necessary to a total of 50 mg. of the ion. Even larger doses have been used in occasional resistant cases. In such instances larger doses not only produced a greater but also a more prolonged reduction of blood pressure.

In some patients, however, the hypotensive effect did not persist beyond six hours. In such cases various drugs were used in an attempt to maintain the hypotensive response, the most effective of which was 1-hydrazinophthalazine (C-5968)* given orally midway between the doses of C6. The initial dose of C-5968 was 25 mg. and this was increased at intervals of 24 hours by increments of 25 mg. until the patient manifested a significant hypotensive response or until side effects such as severe palpitation occurred. The effective dose of C-5968 usually varied between 50 and 150 mg. Like C6 this drug usually could not be given more often than every 12 hours without the appearance of side effects, particularly head-

* Generously supplied by Frederick Yonkmann, M.D., Ciba Pharmaceuticals, Summit, N. J.

aches, as well as the development of tolerance. A complete description of the results obtained with C-5968 will be reported elsewhere.¹³

RESULTS IN HYPERTENSIVE DISEASES

Thirty-two patients have been treated for periods varying between one and five months. All except one were hospitalized prior to and at the onset of treatment. Fourteen of these cases exhibited malignant hypertension, two had chronic glomerulonephritis, while the remaining patients had varying degrees of sustained diastolic blood pressure of 110 mm. Hg or higher. The two patients with chronic glomerulonephritis and uremia exhibited reductions of blood pressure and temporary symptomatic improvement, but died within one and two months respectively of their uremia.

Malignant Hypertension

Of the 14 cases of malignant hypertension, six showed a good result following the use of C6, four exhibited remissions using C6 and C-5968 in combination¹³ and four, three of whom had advanced renal failure, had a poor result. All except one of these patients also were administered diets containing 200 to 500 mg. of sodium per day. However, this probably was not necessary in all cases and in each patient it was possible to demonstrate the hypotensive effect of hexamethonium in the results obtained.

Case 1. R. D., a 52 year old housewife, was first seen with malignant hypertension one year previously. Treatment with a diet containing 200 mg. of sodium per day and Anatensol* resulted in a remission lasting approximately eight months. The malignant phase then gradually returned despite treatment and in November 1950 the patient once again exhibited marked neuroretinitis. The blood pressure, recorded three times daily either by the patient's husband or a visiting physician, was relatively fixed at 250/140. There was weight loss from 110 to 94 pounds, anorexia, nausea and vomiting, constant headache, and nocturia five to six times. The blood nonprotein nitrogen was 39 mg. per 100 cc.

Hexamethonium was begun on Nov. 2, 1950, 25 mg. every six hours, with an immediate fall

of blood pressure to approximate levels of 190/120 (fig. 1). The dose was reduced to 25 mg. every 12 hours, but because of elevations of pressure in the morning, the frequency of doses was increased to every eight hours. During the first two weeks there was severe obstipation, nausea, vomiting and faintness. However, all symptoms began to regress and within two months the fundi had cleared completely except for residual scars. After 14 weeks the number of injections was reduced to two a day, but the dose was increased to 38 mg. with maintenance of reduced levels of blood pressure (fig. 1).

After five months of treatment with C6, the patient had a good appetite and weighed 106 pounds. The nocturia, headaches and nausea disappeared. Following each injection of C6 she found it necessary to remain supine for one to two hours because

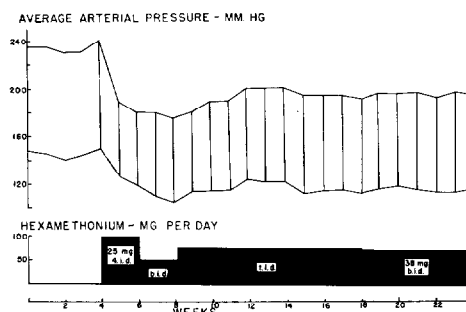


FIG. 1. Chart of the average arterial blood pressure and dosage of hexamethonium in case 1, R. D., a white woman, aged 52 years, with malignant hypertension. Each point in the chart of arterial pressure represents the average of at least 28 separate determinations, all being recorded with the patient in the supine position. See text for further details.

of the postural hypotension. Throughout treatment the blood pressure levels fluctuated, markedly dropping one-half to one hour after each injection and then slowly rising until the next dose of C6. Even after five months, during a single day it was not unusual for the recorded pressures to vary between 160/95 to 210/130 mm. Hg. Because of persistent constipation, laxatives daily and enemas several times per week were required until Urecholine plus mild laxation were introduced.

Case 2. T. M. a 52 year old man, was admitted with a blood pressure of 260/170. There was extensive neuroretinitis with many hemorrhages and exudates in the fundi. The blood nonprotein nitrogen was 48 mg. per 100 cc. The patient was placed on a 200 mg. low sodium diet and was given 10 mg. of C6 intravenously on the day of admission. Within five minutes after the drug had been given the blood pressure fell from 260/170 to 100/80 supine. Despite this sudden and profound hypotensive response the patient noted only a moderate sensation of faintness. When this dose was repeated every four hours

* Purified extract of veratrum viride. E. R. Squibb & Sons, New York, N. Y.

the blood pressure rose and, despite elevation of dosage to 25 and even 50 mg. repeated every four hours, the general level of blood pressure returned to nearly control values (fig. 2). The interval between doses was then increased to 12 hours and this was followed by a fall in pressure to normotensive levels. After three weeks the blood pressure fell to 80/60 and the patient complained of marked faintness. Hexamethonium was discontinued and the patient was given 1000 cc. of saline intravenously. He improved immediately, the blood pressure rising to 130/100. The sodium content of the diet was increased to 500 mg. per day. C6 was omitted for the next 10 days and the blood pressure gradually rose

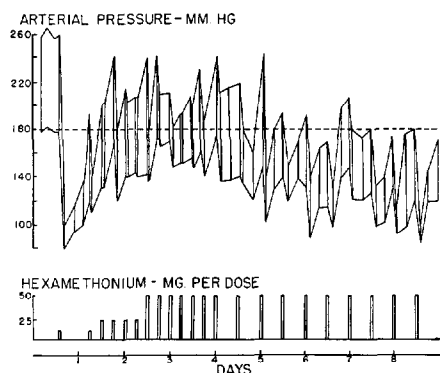


FIG. 2. Chart of the arterial pressure and dosage of hexamethonium in case 2, T. M., a white man, aged 52 years, with malignant hypertension. All blood pressures were recorded with the patient in the supine position. Note (1) the marked hypertensive response to a small initial dose of C6, (2) the apparent development of tolerance when doses were administered at frequent intervals, (3) the return of a significant hypotensive effect when the doses of C6 were separated by an interval of 12 hours, and (4) the typical marked fluctuations of blood pressure during each day while under treatment. See text for further details.

to a level of 170/120. The drug was again given in doses of 10 mg. every 12 hours, the blood pressure falling to average values of 140/100, where it remained for the succeeding month. The hemorrhages and exudates disappeared from the optic fundi although slight papilledema still remained. At the end of the next month the papilledema had cleared completely, the nonprotein nitrogen was 36 mg. per 100 cc. and the patient was ambulatory and felt considerably improved.

Hypertension Other Than Malignant

There were 16 patients in this group, of whom 10 exhibited a continued, average reduction of blood pressure greater than 25 mm. Hg systolic and 10 mm. Hg diastolic. Of this

number seven exhibited sustained reductions of average pressure varying between 40 and 60 mm. Hg systolic, and six of these maintained reductions of diastolic pressure varying between 20 and 40 mm. Hg. Two of the patients who had a good result exhibited grade III changes in the fundi; all of the others being grade II. Of the patients who exhibited a poor response, three exhibited grade III changes, two grade II, and one manifested grade I fundi. Thus, there was no relationship between the severity of the hypertension and the therapeutic result obtained.

Some of the cases manifesting poor results were treated in the earlier stages of the investigation. They were failures either because resistance to the hypotensive effects developed quickly, or the duration of the hypotension was brief or was insignificant in the supine position. Several of the more recently treated patients, who appeared to be resistant to C6 alone, have exhibited a satisfactory hypotensive response when the dosage was raised and/or when C-5968 was added to the treatment regimen.¹³

DISCUSSION

The results obtained to date with the use of hexamethonium in the treatment of hypertension are in essential agreement with the prior observations of Smirk¹⁴ and other investigators.⁵⁻⁸ The combined experience of these various studies leaves little doubt that hexamethonium provides a method for reducing blood pressure in a large percentage of hypertensive patients, and that this reduction frequently is accompanied by relief of some of the signs and symptoms associated with the disease. The ability to induce a significant therapeutic response in 10 of the 14 cases of malignant hypertension either with C6 alone or in combination with a low sodium diet and/or C-5968 represents in our experience a higher percentage of remissions than would be anticipated with other known methods of treatment.

The advantages of C6 are its ability to produce and to maintain for long periods a significant hypotensive response in a high percentage of patients, its rapidity of action and simplicity of administration. The disadvantages are (1)

the danger of severe hypotensive reactions due to injudicious dosage administration in the early phases of treatment, (2) the frequent development of constipation and occasionally paralytic ileus, and (3) the inability to obtain a stable level of hypotension throughout the 24 hour period in many patients. Finally, unless the technic of administering oral therapy can be improved, the necessity for continued hypodermic injections imposes a hardship on the patient. Recent evidence suggests that large amounts of hexamethonium dichloride (0.5 to 2.0 Gm. of the ion) given as a single daily oral dose administered at bedtime may be more effective than divided oral dosage.¹⁵

The most dangerous of the "toxic" reactions is the extreme hypotension that may follow the initial dose of the drug. A fatality has been reported after C6¹⁶ and serious hypotension has occurred also following the less potent and shorter acting ganglionic blocking agent, tetraethylammonium.¹⁷ In both of these reported cases, epinephrine was used to combat the hypotension. Epinephrine has a vasodilator component and, after the pressor response has subsided, the blood pressure does not fall directly to normal, but rather there is a period of hypotension.¹⁸ Epinephrine also induces marked vasodilation in skeletal muscle¹⁹ and, in contrast to norepinephrine and related drugs, produces a decrease rather than an increase in total peripheral resistance.²⁰ In addition, the ganglionic blocking agent tetraethylammonium increases the sensitivity of the myocardium to epinephrine-induced arrhythmias in dogs under cyclopropane anesthesia.²¹ As a result of their study, Stutzman and his co-workers²¹ concluded that "epinephrine is contraindicated as a pressor agent after tetraethylammonium chloride." They recommend that phenylephrine (Neosynephrine) be used for this purpose.

The most successful and the safest procedure for treating the collapse reactions following the administration of C6 was to elevate the foot of the bed in order to maintain the cerebral circulation. In addition, further elevation and passive exercise of the lower extremities facilitated diversion of blood into the central circulation.

These severe hypotensive responses almost always occur only after the *initial* injection. Hence, if care is used at this time such reactions should be avoidable. Since we have utilized the method of administration outlined in the "dosage adjustment" section of this paper, severe collapse reactions have not been encountered. The importance of determining the effective initial dose in each case is emphasized by the observation that one patient exhibited a significant hypotensive response after only 3 mg. of C6 ion had been administered intravenously. If 5 or 10 mg. had been injected the patient almost certainly would have had a severe hypotensive reaction. On the other hand some cases have exhibited little hypotensive response in the supine position after an initial dose of 50 mg.

The concomitant administration of a parasympathomimetic agent to alleviate the constipation, ileus, dry mouth and difficulty in urination produced by C6 represents one application of the general principle of circumventing undesirable side effects by utilizing antagonistic pharmacologic agents which, however, do not interfere with the desired therapeutic action. Since parasympathomimetic agents have vasodilator properties they may be expected to enhance the hypotensive effect of C6.

The therapeutic regimen of alternating doses of C6 and C-5968 also seems representative of another principle of hypotensive drug therapy. In our experience all vasodepressor agents produce varying degrees of tolerance. By utilizing alternately agents with different loci of action the development of tolerance to any single agent may be considerably delayed.

Smirk has taught his patients to self-administer hexamethonium by injection in the home.¹⁴ This procedure has been applied successfully in the present study, and, in addition, in many instances a member of the family or the patient has been taught to record the blood pressure. By such frequent measurements of arterial pressure under varying conditions a far more precise indication of the effect of treatment has been obtained.

It should be emphasized that the results of treatment with C6 reported herein are of a

preliminary nature since none of the patients have been treated continuously for longer than five months. In addition, the most effective method of administering the drug or of combining it with other hypotensive procedures cannot be considered to be finally settled. Finally, because the method of administration outlined herein requires repeated hypodermic injections and frequent observation of the patient, at least in the initial phases of treatment, it would seem to be indicated only in the more severe and resistant cases of hypertension.

SUMMARY AND CONCLUSIONS

Hexamethonium has been administered continuously for periods of one to five months by subcutaneous injection to a series of 32 hypertensive patients with the following results:

1. In 14 cases of malignant hypertension, six have undergone a remission of the malignant phase while four others have exhibited remissions with the addition of 1-hydrazinophthalazine (C-5968) administered orally midway between the doses of C6. Four patients, three of whom had advanced renal failure, did not respond to C6 alone or in combination with other drugs. Two additional patients who had advanced chronic glomerulonephritis exhibited hypotension and symptomatic improvement but died of progressive uremia.

2. In 16 patients with less severe degrees of sustained hypertension, six have shown sustained reductions of arterial pressure after hexamethonium alone, four have responded to a combination of C6 and C-5968 while six others failed to maintain a sustained hypotensive response. Most of the latter cases were treated in the early stages of this investigation when the doses were too frequent and too small.

3. The effective hypotensive dose of C6 ion by subcutaneous injection varied between 10 and 100 mg. Small doses usually lowered the blood pressure after the initial injection but gradually increasing doses were required over a period of days or weeks to attain a stable effective dosage level. C6 was administered at intervals of 8 or 12 hours.

4. Undesirable reactions consisted of (1) occasional severe reductions of blood pressure

occurring almost entirely only after the initial injection of C6, (2) postural hypotension diminishing in severity with prolonged treatment, (3) gastrointestinal atony producing constipation occasionally with paralytic ileus and, rarely, (4) difficulty in urination. Methods for circumventing most of these reactions are described.

5. Hexamethonium administered orally in doses up to 1.0 Gm. of the ion to a few patients appeared to be less effective and more unpredictable than parenteral administration.

6. The most effective and best tolerated treatment for the largest number of hypertensive patients was the following: (1) parenteral administration of C6 at intervals of 12 hours in doses of 10 to 75 mg. of the ion depending upon the patient's response, (2) oral ingestion of 50 to 150 mg. of C-5968 midway between the doses of C6 and (3) a diet containing 200 to 500 mg. of sodium per day.

ADDENDUM

After 10 months of continuous treatment all the cases in this series who had responded favorably are maintaining a significant hypotensive effect and they remain clinically improved, except for one patient with malignant hypertension who died suddenly due to a coronary occlusion. In some cases it has been necessary to elevate dosages to as high as 150 mg. of C6 ion in order to overcome tolerance but this has been accomplished without adverse side effects.

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